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54 Oral pharmaceutical preparation for pain therapy

57 The preparation for oral administration contains an opioid and an opioid antagonist, whereby the opioid is

subject to delayed release after administration, but the opioid antagonist has lower or no delayed release properties. It is hereby possible to eliminate the side effects of the opioid, particularly constipation, so the analgesic effect of the opioid is reduced. The preparation is particularly suitable for long-term therapy.

DESCRIPTION

The invention relates to an oral pharmaceutical preparation for pain therapy which contains an opioid and an opioid antagonist.

There is a long-standing need to reduce or completely eliminate the significant side effects of strong analgesics while minimally impairing their analgesic effect.

In particular, the opioids, which have long been known as good analgesics, are accompanied by such serious side effects especially in long-term therapy, that they sometimes have to be discontinued in order not to compromise overall therapeutic success. As has been subsequently demonstrated, the risk of dependence can be disregarded; and respiratory depression also occurs very rarely. But the constipation provoked by opioids, particularly morphines, can be so serious that opioid therapy cannot be continued.

Attempts have therefore been made to specifically reduce the opiate side effects.

US-PS 4 769 372 discloses that opioids with an opioid antagonist, preferably naloxone, can be orally administered together, i.e. concomitantly, or given in a combination preparation. This enabled the constipating effect of orally administered opioids to be significantly decreased without a noticeable reduction in the analgesic effect. However it

was not possible to eliminate the constipation experienced by patients even after clinical adjustments. It was only possible to optimise the relationship between the constipating effect and the analgesic effect, with both being reduced but the constipation being reduced to a greater extent. A particular disadvantage is that the constipation remains too serious when very high opioid doses are administered, as is required during long-term pain therapy, and therapy is adversely affected, if not impaired.

US-PS 4 457 933 also discloses that naloxone can be administered concomitantly and in combination with strong analgesic substances such as oxycodone, propoxyphene and pentazocine, but this is with the specific goal of reducing the potential for opioid misuse during oral or parenteral administration, without aiming to prevent constipation.

The object of the present invention however is to more effectively reduce constipation as a side effect in opioid pain therapy than hitherto without impairing the analgesic effect. At the same time, simple and safe use of the preparations is assured which is not too onerous for patients even at high opioid doses in long-term therapy.

The present invention for an oral pharmaceutical preparation of the above mentioned type achieves this object by having the opioid present in a delayed release preparation and the opioid antagonist present in a preparation from which it is released without any delay.

It was surprisingly discovered that the early release of the opioid antagonist combined with the delayed release of the opioid in targeted delivery over a longer period resulted in the incidence of constipation not only being significantly reduced, but being practically preventable from the outset. Both the delayed release of the opioid and

the smaller or lack of delayed release of the opioid antagonist together contribute to the effect which is the object of the invention.

According to the invention the opioid antagonist is absorbed in the upper section of the intestine, while the opioid can reach the lower section of the intestine due to its delayed release, is then absorbed in all sections of the intestine and is transported to the brain in the blood stream. By means of the invention, appropriate administration of the preparation over time enables both the opioid and the antagonist to be maintained at a suitable level at their corresponding sites of action, with constipation being prevented or eliminated and with no impairment of analgesic effect.

Another advantage of the invention is that the dosing of opioid and antagonist does not have to be determined by adjusting doses in hospital, as was sometimes1 necessary with existing combinations, but can be achieved through the sustained release properties. The invention is particularly advantageous for long-term pain therapy when it is necessary to administer very high doses due to the course of the disease, e.g. for tumour patients at a late stage and/or the onset of tolerance for the opioid. In such cases a partial decrease of constipation, achievable using known substances, is not possible since slight constipation maintained over a long time can result in the same end result as severe constipation, i.e. complete intestinal obstruction.

A final advantage is the use of a safe administration method, so long-term pain patients no longer need to be seen in a hospital setting. With concomitant or regular administration of several individual preparations this would not be possible.

It has been shown to be particularly advantageous if the ratio of opioid antagonist to the opioid contained in a therapeutically effective quantity has a ratio of naloxone to morphine or the pharmacodynamic equivalent thereof that is less than or equal to 20 : 1.

The development of the invention envisages that the antagonist is higher dosed than the opioid, preferably in a ratio expressed as above between 15 : 1 and 1 : 1, with a particularly preferred ratio of around 10 : 1.

The opioid can preferably be morphine or methadone. The invention is not limited to these substances however, but other opioids can also be used. In particular instead of morphine or methadone, analogues that essentially have the same therapeutic action may be used, such as derivatives or salts. Naloxone is the preferred opioid antagonist. Other antagonists can be used however, particularly if they have no or only slight antagonistic effect towards analgesia when administered orally.

The sustained release component within the preparation can be a combination of the opioid active ingredient with suitable release retarding excipients, for example obtained by mixing and pressing the excipient or excipients together with the opioid. A suitable formulation for this type of preparation is described in DE-PS 22 24 534. Other sustained release excipients can be used.

The preparation for delaying the release of the opioid antagonist can be formulated so the retarding excipients and/or their concentration are selected so retardation of the antagonist is lower than that of the opioid. The two different sustained release components can then, for example, be granulated and mixed to form a powder, pressed together in a two layer tablet, or encapsulated separately.

It is also possible to micro-encapsulate the opioid with diluents and excipients, such as lactose, talc or maize starch, and partial microencapsulation of the antagonist is also possible.

Further advantageous embodiments of the invention are described in the sub-claims.

The following examples illustrate the invention in more detail:

Example 1

Morphine/Naloxone

Cetyl alcohol	150 parts by weight
Hydroxyethyl cellulose	50 parts by weight
Morphine	20 parts by weight
Naloxone hydrochloride	400 parts by weight

A sustained release morphine preparation is made according to the method described in DE-PS 22 24 534.

For this purpose cetyl alcohol is melted in a water bath and finely granulated through a sieve. Freshly granulated hydrated hydroxyethyl cellulose is also prepared by hydrating 50 parts by weight hydroxyethyl cellulose with 2 to 3 parts by volume of water per weight part and then granulated. The morphine is either mixed in with the alcohol or the hydroxyethyl cellulose or divided between the two components. The two granulates containing the morphine are dried and then mixed with the naloxone hydrochloride.

This mixture can be administered as a powder, pressed to tablets together with tabletting excipients or filled into capsules.

Instead of the alcohol and hydroxyethyl cellulose mixture, other retarding excipients can be used. For example the opioid could be adsorbed onto an adsorbent inside the preparation such as cholestyramine resin. The use of different retarding substances results in different release profiles, but they can be adjusted or balanced by appropriate variation of the proportions.

Example 2

Morphine/Naloxone

Retarding excipients, i.e. cetyl alcohol and hydroxyethyl cellulose in a ratio of 3 : 1, prepared as in Example 1 and granulated	30 parts by weight
Lactose	35 parts by weight
Talc	10 parts by weight
Morphine	20 parts by weight
Tabletting excipients: talc and magnesium stearate	to 100 parts by weight

The granulate mixture of retarding excipients is mixed with the morphine, diluents and excipients, dried and pressed to form 100 mg tablets.

Naloxone hydrochloride	200 parts by weight
Lactose	95 parts by weight
Magnesium stearate	5 parts by weight

The naloxone is mixed with the excipients and pressed as a second layer onto a 300 mg sustained release morphine tablet. Two layer tablets of 400 mg are obtained.

Example 3

Morphine/Naloxone

Retarding excipients	60 by weight
Morphine	20 parts by weight
Naloxone hydrochloride	120 parts by weight

The morphine is made into a granulate mixture with retarding excipients as in Example 1 or 2. the naloxone is micro-encapsulated using known methods with gelatine. The granulate and the micro-encapsulated naloxone are filled into capsules in the above ratios.

Example 4

Dihydrocodeine/Naloxone

Retarding excipients	90 parts by weight
Dihydrocodeine	15 parts by weight
Lactose	50 parts by weight
Maize starch	20 parts by weight
Naloxone hydrochloride	225 parts by weight

Retarding excipients are intimately mixed with the dihydrocodeine and granulated in the usual way. The granulate is dried, mixed with the diluents and naloxone, and filled into capsules. The dihydrocodeine dose can be varied according to capsule size.

Example 5

Oxycodone/Naloxone

Retarding excipients	100 parts by weight
Oxycodone	100 parts by weight
Naloxone hydrochloride	100 parts by weight

Lactose	65 parts by weight
Talc	40 parts by weight
Magnesium stearate	to 400 parts by weight

The oxycodone is prepared in the usual way with the retarding excipients, and the granulate is dried. The naloxone is intimately mixed with the diluents and magnesium stearate. This mixture is mixed with the granulate and tabletted. The mixture can also be filled into capsules or processed into film tablets.

Example 6

Propoxyphene/Naloxone

Retarding excipients	100 parts by weight
Propoxyphene	10 parts by weight
Naloxone hydrochloride	120 parts by weight
Lactose	to 300 parts by weight

The propoxyphene is prepared in the usual way with 70 parts retarding excipients and the naloxone with 30 parts retarding excipients, and the mixture granulated. The granulates are mixed with lactose and filled into capsules.

Example 7

Pentazocine/Nalmefene

Retarding excipients	80 parts by weight
Pentazocine	100 parts by weight
Nalmefene	100 parts by weight
Lactose	40 parts by weight
Talc	20 parts by weight

The pentazocine is prepared with the retarding excipients as in the above examples and granulated, mixed with nalmefene and the excipients and filled into capsules or pressed with tabletting excipients into tablets.

Example 8

Morphine/Naloxone granulate for high doses

Retarding excipients	30 parts by weight
Morphine	10 parts by weight
Naloxone	100 parts by weight

10 parts cetyl alcohol are melted and finely granulated. The morphine is mixed with the granulated melt. The mixture is blended with 20 parts by weight hydroxyethyl cellulose, which has been hydrated with 2 to 3 parts by volume of water and freshly granulated. The granulate mixture is dried, mixed with the naloxone and processed to a coarse granulate with added aqueous starch solution in the usual way.

Example 9

Morphine/Naloxone syrup

A quantity of adsorbent saturated with morphine (e. g. a resin such as cholestyramine resin or suitable silica gel or Sasil) holding 1 g morphine is removed and mixed together with 5 to 15 g naloxone hydrochloride and made up to 100 ml syrup. If necessary the mixture is emulsified by adding an emulsifying agent.

PATENT CLAIMS

1. An oral pharmaceutical preparation for pain therapy which contains an opioid and an opioid antagonist, **characterised in that** the opioid is present in a sustained release preparation and the opioid antagonist is present in a preparation from which it is released with little or no delay.

2. Preparation according to claim 1, characterised in that the opioid antagonist is present in a ratio to the opioid, corresponding to a ratio of naloxone to morphine or the pharmacodynamic equivalent, of less than or equal to 20 : 1.

3. Preparation according to claim 2, characterised in that the specified ratio of antagonist to opiate lies between 15 : 1 and 1 : 1 and is preferably about 10 : 1.

4. Preparation according to one of the claims 1 to 3, characterised in that the opioid is morphine or methadone, or analogues with the same therapeutic action.

5. Preparation according to claim 4, characterised in that the opioid is morphine in a dose between 20 and 5000 mg.

6. Preparation according to one of the claims 1 to 5, characterised in that the opioid antagonist is naloxone, or an analogue with the same therapeutic action.

7. Preparation according to one of the claims 1 to 6, characterised in that the delayed release of opioid achieved by the preparation is over ca. 5 to 24 hours.

8. Preparation according to one of the claims 1 to 7, characterised in that the preparation for sustained release contains a combination of the opioid active ingredient with suitable retarding excipients, for example obtained by mixing and pressing together the opioid with the excipient or excipients.

9. Preparation according to claim 8, characterised in that the sustained release preparation also contains a combination of opioid antagonist with suitable retarding excipients, whereby the retarding excipients and/or their concentration is selected so the delayed release of the antagonist is less than that of the opioid.

10. Preparation according to one of the claims 1 to 7, characterised in that the sustained release preparation consists of a microencapsulation of the opioid together with any diluents and excipients and part microencapsulation of the antagonist with any diluents and excipients.

11. Preparation according to one of the claims 1 to 10, characterised in that the preparation is made in a dosage form suitable for sustained release oral administration, such as tablets, capsules, powder, syrup or drops.